Arq Neuropsiquiatr 2003;61(3-B):842-847

LEPTOMENINGEAL DISSEMINATION OF PILOCYTIC ASTROCYTOMA AT DIAGNOSIS IN CHILDHOOD

Two cases report

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ABSTRACT - Pilocytic astrocytoma (PA) is a benign tumor that rarely spread along the neuraxis. At the moment there are no more than five cases of leptomeningeal dissemination (LD) from PA at diagnosis described in the literature. Different patterns of presentation or recurrence may be noted: local recurrence, malignant transformation, multicentric disease or metastatic disease. LD and multicentric disease can be distinct pathological entities. We report two cases and analyse literature, emphasizing leptomeningeal spread at presentation. Hydrocephalus, biopsy and parcial ressection are likely to be favorable factors to the occurrence of LD. Otherwise, LD may be part of natural history of PA, as evidenced by its ocurrence in non-treated cases.

KEY WORDS: pilocytic astrocytoma, leptomeningeal dissemination, multicentric disease, cerebrospinal fluid, metastasis, radiation therapy, chemotherapy, hydrocephalus.

Disseminação leptomeníngea de astrocitoma pilocítico ao diagnóstico: relato de dois casos.

RESUMO - Astrocitoma pilocítico (AP) é tumor benigno que raramente se dissemina ao longo do neuroeixo. Até o momento não há mais que cinco casos de AP que se tenham apresentado com disseminação leptomeníngea (DL) descritos na literatura. Diferentes padrões de apresentação ou recorrência podem ser observados: recorrência local, transformação maligna, doença multicêntrica ou doença metastática. DL e doença multicêntrica podem ser entidades diferentes. Relatamos dois casos e analisamos a literatura. Hidrocefalia, biópsia e ressecção parcial são provavelmente fatores predisponentes à DL. Por outro lado, DL pode ser parte da história natural de AP, como pode ser evidenciado pela sua ocorrência em casos não tratados.

PALAVRAS-CHAVE: astrocitoma pilocítico, disseminação leptomeníngea, doença multicêntrica, líquor, metástases, quimioterapia, radioterapia.

Pilocytic astrocytoma (PA) is a benign subset of gliomas with an excelent prognosis[1] and that rarely spread along the neuraxis. Leptomeningeal dissemination (LD) of primary central nervous system (CNS) tumors in children has been reported mainly in ependymomas, germ-cell tumors, primitive neuroectodermal tumors, high grade gliomas[2-9]. Low grade gliomas dissemination has been documented in few cases[1,2,5,6,9]. Leptomeningeal dissemination of pilocytic astrocytoma in children is much more uncommon with 32 cases reported in the literature[1,2,6,7,9-24]. These include only five with LD at diagnosis[13,17-19]. Dissemination patterns, clinical picture, treatment and outcome are still poorly understood.

We reported two cases evaluated by the child neurosurgery team at Hospital das Clínicas of São Paulo University Medical School that presented LD at diagnosis, enhancing clinical, diagnoses, management and prognosis features.

CASES

Case 1. A girl, 11 years old, had a history of headache and vomiting for four months. One week before hospital admission she presented mental confusion. Computed tomography (CT) scans revealed hydrocephalus and two tumoral masses in ventricular spaces, at right frontal horn and at left occipital horn (Fig 1). Total resection of both lesions was performed. Cerebrospinal fluid (CSF) cytologic examination was positive for neoplastic cells. Pathologic examination showed fusiform cells with wavy fibrillary processes and Rosenthal fibers and confirmed the diagnosis of PA (Fig 2). Ventriculoperitoneal shunting was carried out for hydrocephalus treatment and patient dischar-

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Received 10 February 2003, received in final form 14 April 2003. Accepted 12 May 2003.

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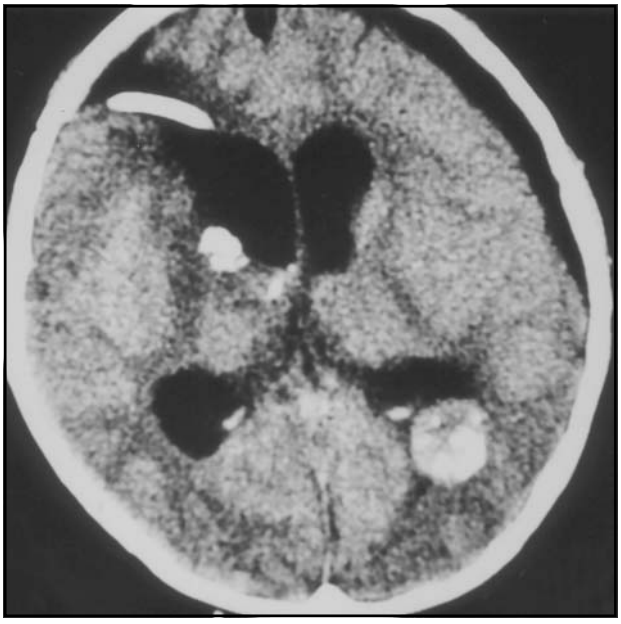

Fig 1. Contrast-enhanced CT scan shows two lesions in ventricular spaces, at right frontal and at left horns, and hydrocephalus.

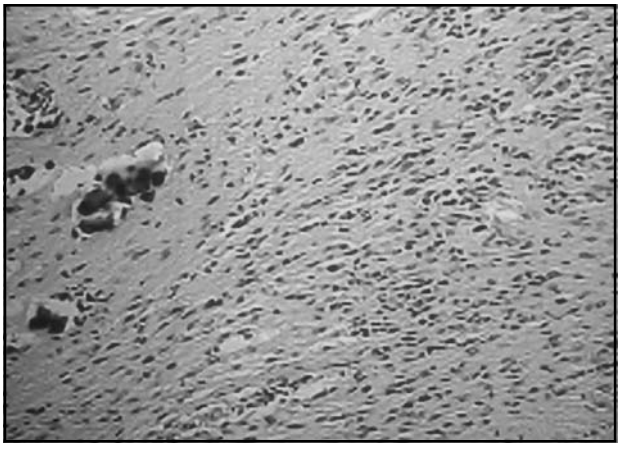

Fig 2. Histological appearance of pilocytic astrocytoma showing fusiform cells with wavy fibrillary processes and Rosenthal fibers.

ged without symptoms. Radiotherapy was proposed but it was refused by her relatives. Four months after discharge, the patient returned with poor general appereance, consciousness impairement, fever, stiff neck and generalized spasticity. CT scan showed diffuse sub-arachnoid enhacement (Fig 3). CSF culture was negative and cytologic examination revealed important pleocytosis with neoplastic cells. Death occured in a few weeks.

Case 2. In February 1994, an eight years old girl was admitted with a four years history of headache, vomiting and visual acuity deterioration. At that period she mentioned stiff neck and occipital pain; neurologic examination showed axial and apendicular cerebellar symptoms, amaurosis and meningismus. The optic disks were atrophic. A hypothalamic syndrome (Russell syndrome) was present and nutritional status was precarious. Magnetic resonance image (MRI) with gadolinium revealed a lesion with cystic and solid parts at the optic nerve and chiasma with multiple tumoral implants on the subarachnoid space and hydrocephalus (Fig 4). Ventriculoperitoneal shunting and stereotactic puncture of the cyst were performed. Histological examination revealed similar features to previous case. Patient underwent radiation therapy (RDT) and was discharged. Surgery was delayed due to poor clinical conditions. Infectious complications caused death after months.

DISCUSSION

Although PA has usually a benign course, it can eventually show a malignant behavior. Different patterns of presentation or recurrence may be noted: local recurrence, malignant transformation, multicentric disease or metastatic spread[1,6,25-30]. Controversy exists about multicentric disease definition. Mamelak defined it as either diffuse subependymal or leptomeningeal dissemination beyond the margins of the primary tumor or as discrete nodular disease separate from the primary tumor mass[1]. However, multiplicity of PAs might be due to the multiple genesis of the tumor instead of tumor spread to the subarachnoid space[12]. LD and multicentric disease can be distinct pathological entities with different pathogenesis and perhaps different clinical features.

LD of PA is uncommon with only few cases reported in the literature. At the moment we can find just

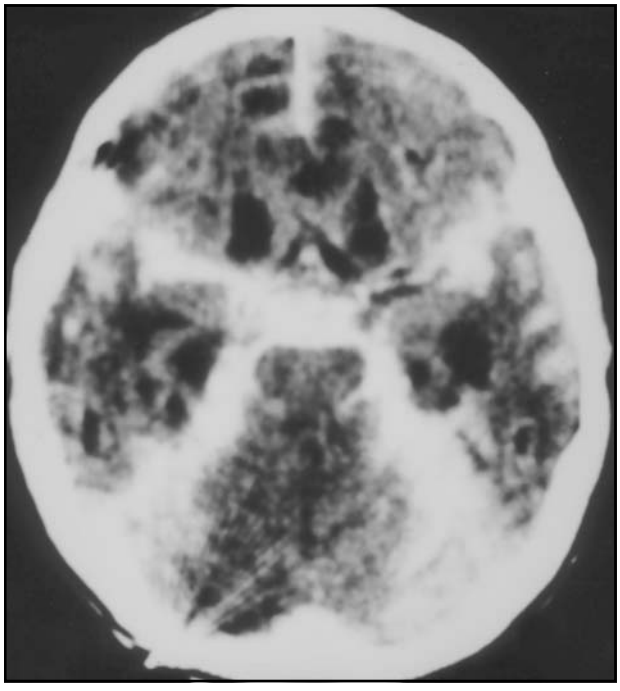

Fig 3. Contrast-enhanced CT scan shows a diffuse sub-arachnoid enhancement.

TABLE 1. LEPTOMENINGEAL DISSEMINATION IN CHILDREN WITH PILOCYTIC ASTROCYTOMA

AUTHOR	AGE AT INITIAL DIAGNOSIS	SITE OF PRIMARY TUMOR	PREDISSEMINATION PROCEDURE	TIMING OF LD	THERAPY FOR LD	OUTCOME
MCLAUGHIN (1976)	08 Ys	III VENTRICLE	-	-	-	DIED
	13 Ys	III VENTRICLE	-	-	-	DIED
	6,5 Ys	III VENTRICLE	-	-	-	DIED
	18 Ys	III VENTRICLE	-	-	-	DIED
AUER (1981)	8 Ys	CEREBELLUM	SURGERY + LOCAL XRT	10 Ds	-	DIED
CIVITELLO (1988)	8 Ys	CEREBELLUM	SURGERY	6 Ys	CHT + CS XRT	ALIVE 1 Ys 5 Mos
	4 Ys 9 Mos	CHIASM	BPS + LOCAL XRT	3Ys 5Mos	SPINAL XRT	DIED 1 Ys 9 Mos
KOCKS (1989)	10 Ys	CHIASM	SURGERY	2 Ys	XRT	ALIVE 1Ys
BRUGGERS (1991)	Mos	CHIASM	SURGERY	AT DIAGNOSIS	CHT	ALIVE
OBANA (1991)	16Mos	CHIASM	SURGERY	8, 5 Ys	CHT	ALIVE 1,5Ys
MISHINA	6 Ys	CEREBELLUM	SURGERY+ LOCAL XRT	6 Ys	CS XRT	ALIVE 2Ys
VERSARI	7 Ys	CHIASM	SURGERY+LOCAL XRT	3 Ys	PARCIAL RES.	DIED 48 Mos
POLLACK (1994)	5 ½ Ys	CEREBELLUM		AT DIAGNOSIS	XRT	ALIVE
MAMELAK (1994)	3 Ys	HYPOTHALAMIC	SURGERY +CHT	-	CS XRT	ALIVE 34 Mos
	9 Mos	HYPOTHALAMIC	SURGERY +CHT	-	CHT	ALIVE 20 Mos
	16 Mos	HYPOTHALAMIC	SURGERY+ XRT	-	CHT	ALIVE 4 Ys
	5 Mos	HYPOTHALAMIC	SURGERY	-	SUBTOTAL RES. + CHT	DIED 32 Mos
	11 Mos	HYPOTHALAMIC	BPS +CHT	-	CHT	DIED 41 Mos

GAJJAR (1995)	3 Ys	HYPOTHALAMIC	BPS	-	CHT	-
	1 6 Ys	HYPOTHALAMIC	BPS	-	RT	-
	11 Ys	TEMPORAL LOBE	SURGERY	-	PARCIAL RES.	-
MCCOWAGE (1996)	8Ys	III VENTRICLE	SURGERY + XRT	2 Ys	CHT	ALIVE 27 Mos
	5 Ys	CEREBELLUM	SURGERY	3 Ys	CHT	ALIVE 10 Mos
	2 ½ Ys	III VENTRICLE	SURGERY	8 Mos	CHT	ALIVE 3 Ys
	7 Ys	CHIASM	BIOPSY	AT DIAGNOSIS	CHT	ALIVE 6 Mos
MORIKAWA (1997)	4 Ys	CEREBELLUM	BPS	AT DIAGNOSIS	SURGERY	ALIVE
JAMJOOM (1998)	-	CEREBELLUM	VPS	2Ys	-	-
TAMURA M (1998)	6Ys	CEREBELLUM	SURGERY	4Ys	SURGERY+ CS XRT	ALIVE 5 Ys
	4Ys	CHIASM	SURGERY+XRT	4Ys	SURGERY+CHT+CS XRT	-
PATT S (1999)	16 Ys	-	SURGERY	4Ys	CHT	TUMOR STABLE
AKAR (2000)	-	CHIASM	-	AT DIAGNOSIS	-	-
FELLGIEBEL (2001)	14Ys	-	SURGERY	8Ys	-	-
FIGUEIREDO (2003)	11Ys	FRONTAL AND OCCIPITAL VENTRICULAR CORNS	-	AT DIAGNOSIS	SURGERY	DIED 06 Mos
	08 Ys	CHIASM	-	AT DIAGNOSIS	SP + BPS	DIED 05 Mos

BPS - BIOPSY; CHT - CHEMOTHERAPY;CS - CRANIOSPINAL; SP - STEREOTACTIC PUNCTION;XRT - RADIATION THERAPY;VPS- VENTRICULO-PERITONEAL SHUNT

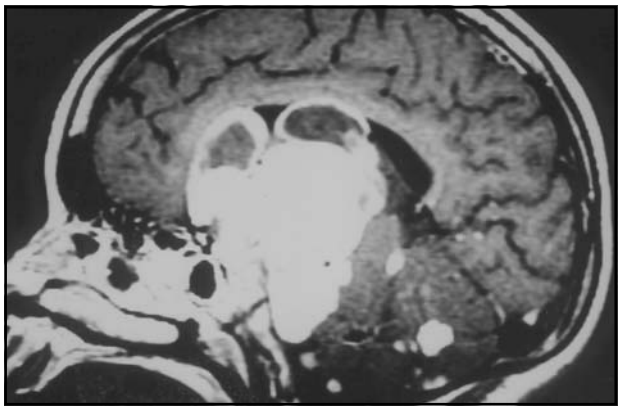

Fig 4. Sagittal T1-weighted MR image obtained after administration of contrast material disclosed a heterogeneous lesion at the optic nerve and chiasm with multiple tumoral implants.

32 cases reported. Incidence of LD of PA is not still determined. Since the use of MRI has become routine in surveying of patients with brain tumors, a sharp increased in number of cases has been noted. Mamelak, analising his series with 90 cases of PA, found an incidence of 12%, including cases of multicentric disease[1]. Gajjar, reviewing low-grade astrocytomas found an incidence of 5,3%[2]. Civitello and associates described 162 patients with low-grade gliomas; six patients (3.7%) had leptomeningeal spread[6]. Pollack found an incidence of 4% of dissemination of low grade intracranial astrocytomas[17].

Spread mechanisms are not well understood. Tumors of any grade arising nearby to CSF pathways may disseminate. Tumoral mass located in the floor of the third ventricle may breach the ependyma and invade ventricular cavity, resulting in to ependymal or leptomeningeal seeding. This is not, however, the only important factor. Tumor cells are able of crossing piamater and invade CSF pathways; their degree of adhesiveness, their metabolic capacities (adhesion molecule production, protease secretion and growth factor pathway activation) and their antigenic factors also may aid leptomeningeal spread[1,2,3,5,27]. A study with CD44 suggests that this adhesion molecule may play a role in astrocytic invasion and adherence[31]. Probably hydrocephalus, biopsy and parcial ressection may also be additional favorable factors, although this remains unproven[1]. When primitive tumor does not arise nearby ventricular spaces, disaggregation of tumoral cells and their entry into the Virchow-Robin space is likely to be the responsible mechanism[15].

LD can occur after a long postoperative period as well as at diagnosis. In fact, LD may be the first sign of disease or of relapse. Clinically, LD can be presented by hidrocephalus, meningismus, worsening of focal deficits, other neurologic deficits and onset of seizures. However, some cases are asymptomatic[1,23].

CSF examination provides unreliable results. In subarachnoid metastatic disease in children, if a single CSF sample is employed, nearly 50% of the patients will not be diagnosed[32,33]. In evaluating 17 children with primary intracranial neoplams for subarachnoid metastatic disease, Kramer found CSF cytologic examination positive in only 29% of the cases[34]. The use of CSF tissue culture can improve standard cytology techniques and almost double the rate of successful diagnosis[35]. Myelography with CT follow-up and MRI with gadolinium was positive in 47% and 65% of the cases, respectively[34]. Thus, MRI with gadolinium seems provide better sensibility and accuracy for LD diagnosis than other diagnostic methods.

Table 1 summarizes related cases. The average age at initial diagnosis of the primary tumor was six years and nine months. Most of the patients were males. Location of primary tumor was in hypothalamus, optic pathways and third ventricle (n=22), cerebellum (n=8) and only one case in the temporal lobe and another in lateral ventricles. Seven patients presented LD at diagnosis (including our patients), what shows that LD may be part of natural history of this tumor. Surgical removal of the primary tumor was total subtotal in most of the cases. Biopsy was employed in 7 patients and RDT and/or chemotherapy were used in 8 and 3, respectively. Only two patients who were submitted to total removal before LD diagnosis and developed subarachnoid spread staied alive during follow-up. Thus total removal may be favorable factor in avoiding dissemination and improving prognosis. However, adjuvant therapy seemed not to change the odds for tumor spread. At histologic examination, there was no pathologic caracteristic sign that allowed prediction of leptomeningeal spread.

LD was treated with chemotherapy (n=14), craniospinal RDT (n= 8) , subtotal resection of primary masses (n=7). There were nine deaths during follow-up, of whose only 2 underwent chemotherapy. McCowage reported treatment of four patients with high dose of cyclofosfamide, including intrathecal therapy, demonstrating three significant tumor responses and one prolonged disease estabilization[18]. These data, however, are not conclusive . RDT seemed not affect prognosis.

We are not certain about which factors are predictive to leptomeningeal spread. Mamelak et al.

found that hypothalamic tumors have a high-risk. However, it seems impossible to distinguish the role played by the site of tumor from that played by the extent of surgical resection, tumor location, hydrocephalus, patient age at diagnosis and type of therapy. Nonetheless, it was possible to draw a profile of the patient at highest risk to developing LD: a child under 4 years old with a primary PA in the hypothalamic region treated with subtotal resection or biopsy followed by adjuvant therapy[1].

The outcome of patients with LD is not well known. Nevertheless, it is likely to be not as good as that of patients with localized recurrence or totaly resected primary disease. However, it is not as bad as the leptomeningeal spread in high-grade gliomas.

In summary, at this time is not possible to predict patients whom will be diseminated disease. More cases are necessary to define optimal treatment and prognosis of this entity. In our opinion, total resection must be performed as often as possible and no adjuvant therapy should be carried out. Children with hypothalamic tumors, subtotal resection, hydrocephalus or those submitted to adjuvant therapy should be followed with cytologic examination of the CSF, which can be also obtained before surgical resection of primary tumor. MRI with gadolinium should also be used during follow-up to allow early diagnosis of dissemination. Radiotherapy and chemotherapy can be used for LD treatment, the second with better support from the literature[18,23,24]. Further controlled studies will define the risks factors, optimal treatment of primary and disseminated disease and prognosis of this rare pathological entity.

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